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Review Article

Diet and Supplements in Cancer Prevention

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Abstract

Cancer is a hereditary multifactorial disease, and due to its rising incidence in both young people and adults along with its substantial burden, oncological emphasis has been placed more on preventive efforts. It has been suggested that several food and lifestyle choices contribute to the onset of cancer, presumably via complex metabolic and inflammatory pathways. Diet is one of the crucial variables in determining cancer risk. In addition, as research intensifies, a more distinct link between diet and patients' molecular alterations is emerging and becoming quantifiable, dispelling the previous conventional wisdom that linked phenotypic changes to dietary variation. Although the evidence is not consistent, appropriate doses of vitamin B12, vitamin D, vitamin C, selenium, folic acid, and antioxidants such as carotenoids have shown a preventive effect in certain types of cancer. However, improper use of dietary supplements in well-nourished people provides no effects or even poses harmful effects to increase the risk of some cancer. Contrarily, other factors like alcohol, obesity, certain fatty acids, and some techniques used for food preparation may increase the risk of cancer. It is now appropriate to make dietary modifications that are consistent with suggestions for preventing cancer incidence with an emphasis on lifestyle improvement including proper management of problems associated with diet, nutrition, smoking, and drinking. However, there is currently a need for more clinical research to demonstrate the safety and effectiveness of using various phytochemicals or plant extracts as dietary supplements to prevent primary stages of cancer.

Introduction

Diet and supplements have a significant impact on the causes and prevention of cancer. It is generally accepted that nutrition plays an important part in cancer incidence. However, even after decades of epidemiological research, several inconsistencies arise as to how exactly specific dietary factors are linked to cancer prevention, limiting the establishment of firm conclusions. Several factors including obesity and excessive consumption of calorific foods, beverages high in sugar content, trans-unsaturated and saturated fatty acids, and red or processed meats are known to increase the risk of developing various tumors, whereas diets high in whole foods such as grains, vegetables, and fruits are thought to reduce this risk. Divisi, Di Tommaso[1] reported that 14% of cancer deaths in men and 20% in women are related to obesity. Alcohol consumption has been linked positively to tumors of the mouth, esophagus, pancreas, liver, and breast, salt or salted foods to gastric tumors, red or processed meats to colorectal or gastric cancers, and aflatoxin to liver tumors.[2] Chemoprevention is characterized clinically as primary, secondary, or tertiary. Primary chemoprevention is appropriate for the general public and those who might be at higher disease risk. For individuals with premalignant lesions that might develop into an invasive illness, secondary chemoprevention is recommended. Nowadays, "primary chemoprevention" generally refers to both primary and secondary chemoprevention. The goal of tertiary chemotherapy, on the other hand, is to stop the progression of an existing disease or the development of a new (second) primary disease in people who have already undergone

Keywords: Diet; Cancer; Epidemiology; Nutrition; Supplements.

Abbreviations: ALL, acute lymphoblastic leukemia; CC, cancer cells; CNS, central nervous system; COX, cyclooxygenase; DHA, docosahexaenoic acid; EC, esophageal cancer; EGCG, epigallocatechin gallate; EPA, eicosapentaenoic acid; IL, interleukin; ITC, Isothiocyanate; KD, ketogenic diet; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids; TNF, tumor necrosis factor; UGI, upper gastrointestinal.

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potentially curative therapy. Numerous dietary phytochemicals are helpful in primary chemoprevention since it has been found that they suppress the initiation phase of carcinogenesis. Additionally, phytochemicals have the ability to alter the molecular processes of metastasis.

Evidence linking diet and cancer

Diet was a prevalent explanation for many diseases even as far back as 168 BC when the physician Galen first highlighted its involvement in cancer growth.[3] Moreover, research has shown a correlation between eating specific foods and elevated cancer risk for decades. However, several factors have made it challenging to conclusively correlate dietary factors to cancer risk. Nonetheless, there is a significant amount of epidemiological data showing a link between specific foods and an elevated risk of developing cancer. The amount, timing, and length of exposure to a bioactive food component all have an impact on cell response, which in turn has an impact on the development of cancer.[4] It is therefore impossible to identify individual compounds as the cause of a specific effect; rather, it is more likely that the effect is the result of the actions of multiple carcinogenic pathways working in combination.[5] Over time, a transition from a reductionist or nutrient-centric approach to a more holistic notion of food that is characterized as dietary patterns has been one of the most significant changes in cancer prevention guidelines, reflecting the present and evolving scientific data. To better reflect what and how individuals eat, it is more useful to examine dietary patterns as a whole rather than focusing on specific nutrients and bioactive substances. In general, the dietary components that work together to affect cancer risk are not isolated nutrients but rather whole foods that people eat. There is mounting evidence linking healthy (as opposed to bad) eating patterns to a lower risk of cancer, particularly colon and breast cancer.[6] For example, meat that has gone through the processes of curing, fermenting, smoking, or salting is considered processed meat. Meats like beef and lamb, which remain red even after being cooked, are typically referred to as "red meat." These red and processed meats contain salt, N-nitroso compounds, heterocyclic amines, heme iron, and polycyclic aromatic hydrocarbons after high-temperature cooking, all of which have been linked to cancer.[7] Although processed beef has been classified as a class one carcinogen, the evidence linking it to gastrointestinal malignancies is limited.

In a recent meta-analysis of 56 cohorts involving over 6 million people, the authors concluded that the absolute effects of red and processed meat consumption on cancer risk were small and that the certainty of the evidence was inadequate.[8] However, the strong evidence connecting processed beef to colorectal cancer has led to its classification as a class one carcinogen.[9] The upper gastrointestinal tract carcinogenesis research has also looked at the possible effect of other dietary variables, such as fresh and salted seafood, fresh and fermented dairy products, and cold and hot beverages.[10] Due to impaired metabolic clearance, heavy alcohol use may increase estrogen levels and breast cancer risk.[11] It also increases carcinogen permeability and inhibits detoxifying. Alcohol has been associated with all types of upper gastrointestinal (UGI) cancer; nevertheless, the mechanisms by which alcohol consumption might cause cancer are beyond the purview of this research. Alcohol consumption is associated with an increased risk of cancer in the oesophagus and liver, two organs located high up in the digestive tract.[12] Due to limited data additional research is needed for the other food categories. On the contrary, pending further research, preliminary findings from the WCRF's Continuous Update Project (CUP) suggest that a diet high in fruits and vegetables may reduce the risk of developing certain types of aerodigestive cancer (%). In addition to reducing cancer risk, there is evidence that a diet rich in fruits and vegetables also reduces the risk of dying from any cause.[13] A healthy diet for cancer prevention meets all of the following criteria:[5] (1) it allows the person to be as lean as possible without being underweight; (2) it is abundant in fruits, vegetables, whole grains, and pulses; (3) it contains little red meat; (4) it excludes processed meats; and (5) it limits salt intake.

According to the World Cancer Research Fund's (WCRF) assessment, there is "convincing" evidence linking certain dietary factors to an increased risk of cancer. These links include aflatoxins and liver cancer, red meat and/or processed meat and colorectal cancer, alcohol and gastrointestinal cancers, and beta-carotene supplements and lung cancer in smokers.[14] Government and prominent non-profit health organizations, such as the American Cancer Society (ACS) and the World Cancer Research Fund/American Institute of Cancer Research (WCRF/AICR), have issued guidelines and recommendations for cancer prevention since the 1980s, with a focus on weight management, physical activity, diet, and alcohol consumption. The WCRF/AICR increased their efforts and recommendations after the first update of the WCRF/AICR guidelines in 2013,[14] recommending the creation of a Continuous Update Project that reports extensively across several cancer types using rigorous systematic review techniques. The American Cancer Society (ACS) regularly publishes the Diet and Physical Activity Guideline to serve as the foundation for its communication, policy, and community initiatives, and ultimately to affect the eating habits of Americans. This recommendation was formulated by a national panel of experts in the fields of cancer research, prevention, epidemiology, public health policy, and more, and it is based on the most recent scientific evidence linking certain dietary and physical activity habits to an increased risk of developing cancer.[15] In 2018, the World Cancer Research Fund International and the American Institute for Cancer Research published their third expert report on cancer prevention.[10] Updated from the 2012 ACS guideline 5, the current ACS Diet and Physical Activity Guideline and recommendations (Fig. 1) are largely based on the WCRF/AICR systematic reviews and Continuous Update Project reports, with additional evidence from systematic reviews and large pooled analyses published since the most recent WCRF/AICR reports.

The accumulation of the eight characteristics of cancer cells—self-sustained in growth signals, insensitivity to anti-growth signals, unlimited replicative potential, evasion of apoptosis, sustained angiogenesis, reprogramming of energy metabolism, evasion of immune destruction, tissue evasion, and metastasis—may be influenced by diet.[16] Dietary manipulation has been proposed as an effective technique for treating tumors. For example, ketogenic diets (KDs) are dietary patterns defined by high fat intake, moderate to low protein consumption, and extremely low carbohydrate intake (50 g), and they may target cancer cell (CC) metabolism in cancer settings, potentially altering tumor treatment and prognosis. KDs efficacy in cancer therapy may be based on a number of pathways, including but not limited to oxidative stress, mitochondrial metabolism, and inflammation, in addition to the previously postulated reduction of glucose/insulin signaling. Although controversy remains over whether KD should be used to treat cancer, therapies that slow or stop cancer growth in early stages, use a broad-spectrum approach, target many signaling pathways, prevent cancer comorbidities such as cachexia and obesity, and have fewer adverse effects are very appealing. KD therapy could be a

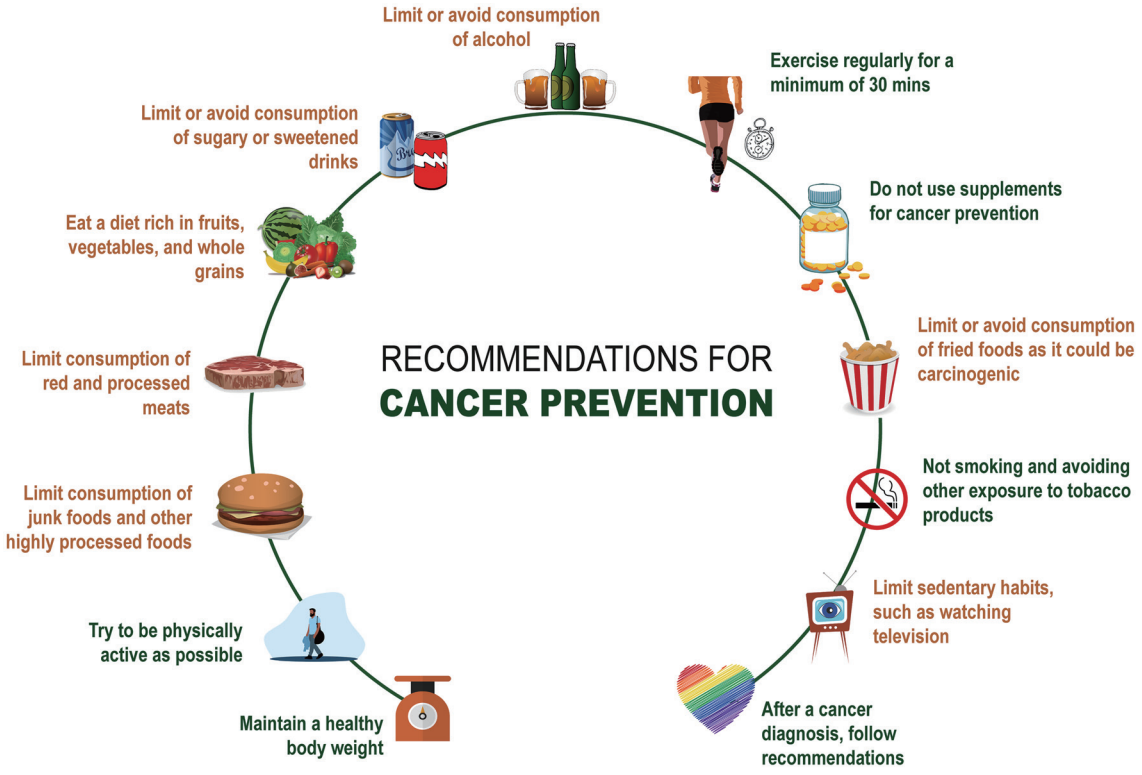

Fig. 1. Recommendations for cancer prevention.

novel, nontoxic, cost-effective adjuvant therapy for cancer patients that exploits tumor metabolic weaknesses beyond glucose/insulin signaling. However, there are limited systematic studies on KD's influence on cancer prevention and progression.[17]

Dietary supplements in cancer prevention

Fatty acids

Dietary fats are typically made up of fatty acids, which can have either beneficial or negative effects on the prevention and treatment of diseases. Since fatty acids naturally occur as combinations of saturated fatty acids (SFA), monounsaturated fatty acids (MUFA), and polyunsaturated fatty acids (PUFA), it is important to evaluate the nutritional and/or therapeutic benefits of dietary fats. A disruption in the metabolism of polyunsaturated fatty acids (PUFAs), which are crucial for maintaining cellular homeostasis, will result in cellular abnormalities and an elevated risk of developing cancer resulting in angiogenesis, cell proliferation, and migration due to the synthesis of imbalanced pro- and anti-inflammatory lipid metabolites.[18] Even though the current status of PUFAs in cancer is somewhat debatable and inconsistent, there is interest in the anti-carcinogenic capabilities of these molecules if administered in the correct doses and intervals. Omega-3 fatty acids have been shown to be effective anti-inflammatories against a wide range of illnesses, including cancer, and are present in small levels in plant-based oils like flaxseed oil as well as marine fatty fish.[19] Eicosapentaenoic and docosahexaenoic acids are the two marine omega-3 fatty acids that have proven anti-inflammatory characteristics, and there is evidence from meta-analysis studies that these acids may reduce the risk of colorectal cancer by 24%.[20] In a randomized controlled trial of patients with familial adenomatous polyposis, a 2 g daily dose of eicosapentaenoic acid (EPA) reduced the number and size of polyps by 20–30%.[21] According to cohort and/or case-control studies, EPA and docosahexaenoic acid (DHA) show promising results in lowering the incidence of breast, prostate, and colon cancer. Animal models employing 7% to 20% omega-3 also showed promising results; however, this level of omega-3 in a diet is likely to be unacceptable to individuals.[22] Uncertainty exists regarding the ideal EPA: DHA ratio or the lowest dose of EPA and DHA that will prevent cancer, but it is likely to be more than 600 mg per day. The majority of phase II preventive trials utilize 1 to 3.3 g of EPA and DHA, which is safe and well tolerated.[22]

Moreover, dietary fat composition has been identified as a key contributor to the gut microbial community structure and data from animal models imply that dietary omega-3 fatty acid intake or increased tissue levels of omega-3 fatty acids are related to an increased abundance of anti-inflammatory bacteria, such as *Lactobacillus* and *Bifidobacterium*.[19] PUFAs like omega-3 and omega-6 can target a wide range of crucial pathways, including transcription factors, nuclear factors, or molecules related to inflammation such as tumor necrosis factor (TNF), IL-1, or IL-6.[23] It has been demonstrated that omega-3 specifically assist the chemoprevention of oral cancer via modulating-catenin signaling pathways[24] or ERK1/2 phosphorylation.[25] According to research by Wang, Zhu,[26] the inhibitory impact of omega 3 fatty acids on the production of eicosanoids from arachidonic acid is the mechanism by which they prevent the development of cancer. Our bodies often create eicosanoids from fatty acids. Arachidonic acid-derived eicosanoids have a pro-inflammatory effect, but eicosanoids made from omega-3 fatty acids have an anti-inflammatory effect. Cyclooxygenase-2 is a crucial enzyme in the synthesis of eicosanoids; when the human

diet contains a higher amount of arachidonic acid, there is an overproduction of Cyclooxygenase, which causes cancer. The overproduction of COX-2 is inhibited by eicosanoids made from omega-3 fatty acids. Human studies in healthy individuals have shown marine PUFA to have little effect on blood inflammatory biomarkers, as a recent randomized experiment in healthy young adults given 0–1,800 mg/day EPA + DHA for 5 months that resulted in a modest drop in serum tumor necrosis factor alpha ($p = 0.08$) showed. However, the administration of 3.4 g/day EPA + DHA ethyl esters (4 g LovazaTM) for 6 months revealed positive modification of many tissue risk biomarkers for breast cancer in premenopausal and postmenopausal women at increased risk of breast cancer.[27,28] Though omega-3 PUFAs don't appear to have any alarming short-term side effects, caution is advised when recommending PUFA supplementation over extended periods due to the possibility of increased adverse effects of omega-3 supplementation, like nausea, fishy belching, loose stools, and prolonged bleeding time particularly due to higher dosage of administration or due to oxidation products or added vitamin E.[29]

Micronutrients

Folate, a water-soluble B vitamin that is ubiquitously found in dark leafy greens, whole grains, nuts, dry cereals, and folic acid, which is a synthetic oxidized form of folate that is commonly used in fortified foods and supplements, has been known to prevent cancer, particularly colorectal cancer. Controversially, according to literature, folate has also been reported to have positive and negative effects since it can sometimes prevent the growth of malignant tumors while in other cases accelerating the spread of cancer.[30] A reduced risk of pancreatic cancer was reported by Fu and Zeng[31] from their meta-analysis study involving 5,654 cases and 1,009,374 individuals. From their meta-analysis study, Ni and Du[32] showed that there is a dose-response relationship between folate and the risk of esophageal cancer (EC).[33] The study found that EC risk was reduced with an increase in serum folate levels when levels were 10 µg/l greater than the lowest standard dosage (3.44 µg/l) and the risk of developing EC is reduced when daily folate intake is 50 µg higher than the lowest reference intake (125.21 µg/day). Studies have also revealed a possible nonlinear link between dietary folate consumption and the risk of breast cancer. Prospective studies revealed a U-shaped connection between dietary folate intake and the risk of breast cancer. Women who consumed 153 µg to 400 µg of dietary folate per day had a significantly lower chance of developing breast cancer than those who consumed less than 153 µg, and more than 400 µg. The case-control studies also indicated a markedly adverse relationship between dietary folate consumption and the incidence of breast cancer. The health of individuals may be negatively impacted by exceeding the recommended dietary intake of folates. Theoretically, there is a possibility of negative effects, including the development of neuropathies due to misdiagnosing cobalamin, the advancement of cancer, and improper CNS development in embryos.[34] According to studies on animals, choline deprivation results in mitochondrial malfunction and an excess of reactive oxygen species, which in turn promotes cancer.

A few investigations on both animals and humans have revealed that dietary choline and folate complement one another in the situation that either of them becomes deficient. In other words, diets low in choline would also result in low levels of tissue folate, which is essential for one-carbon metabolism and DNA synthesis.[35] Excessive formation of free radicals and reactive oxygen species is one of the many mechanisms that could lead to carcinogenesis and is a key mechanism of cancer cells.[36] Studies have linked selenium metabolism genetic variations to the development of complex diseases like cancer. Kipp[37] observed that selenoproteins most likely act as a mediator for the effects of sufficient selenium concentrations on tumor formation. Selenoproteins appear to limit tumor development during the initiation phase by protecting cells from oxidative DNA damage, but they may instead promote the growth of tumor cells that have already formed and lower the likelihood that patients will survive. The study by Hughes and Fedirko[38] indicated that a selenium status below 80 µg/L could be a risk factor for colorectal cancer risk as elevated selenoprotein concentrations were inversely connected with colorectal cancer risk, which correlated more closely in women than in men. The usage of antioxidant supplements has been linked to a lower risk of ovarian cancer development due to their highly inflammatory nature.[39] This association may have arisen because the form of selenite used in supplements forms endogenous selenium nanoparticles, inhibits glycolysis, and leads to mitochondrial malfunction, autophagy, and cytoskeletal depolymerization.[40] The antioxidant properties of vitamins C (ascorbic acid), A (carotenoids and retinoids), and E (tocopherol) are known to delay or prevent oxidation and lower the concentration of free radicals in the body (de Carvalho et al., 2019). It is reported that certain vitamins, such as folate, beta carotene, vitamin D3, and vitamin B6, have antitumoral effects against breast cancer and breast cancer recurrence by preventing its growth, invasion, metagenesis, and angiogenesis.[41]

There are several theories regarding vitamin C's antitumoral mechanism. Vitamin C—or ascorbic acid—when used intravenously in pharmacological amounts acts as a pro-oxidant and increases the production of hydrogen peroxide, which represents one significant potential mechanism of action of vitamin C. Oral vitamin C supplements may work well to prevent the onset of some types of malignancy, especially in people who may have genetic abnormalities like the ten-eleven translocation proteins (Tets) that predispose them to cancer. Preclinical trials where the onset of acute myelogenous leukemia (aML) was demonstrated to be inhibited by oral ascorbate administration provide evidence that vitamin C may prevent or postpone the development of cancer.[42] Similarly, administering oral ascorbate seven days prior to the implantation of cancer cells reduced the growth of tumors in a lymphoma xenograft model.[43] Ascorbate plasma concentrations are frequently lower in cancer patients than in healthy persons. Over 9,000 lung cancer cases were included in a meta-analysis of 21 studies, which found a correlation between a person's risk of lung cancer and their intake of vitamin C. Male adults in the US who consumed 100 mg of dietary vitamin C daily had a 7% lower chance of developing lung cancer;[44] and a similar dose is also linked to a lower mortality rate of women with breast cancer.[45] An inverse linear association between dietary vitamin C consumption and prostate cancer risk was found in a dose-response analysis, with a 150 mg/day dietary vitamin C intake conferring the lowest risk in a meta-analysis study.[46] The reactive oxygen species produced by this hydrogen peroxide can have lethal effects on cancer cells. Another potential mechanism of action is vitamin C's possible impact 2-oxoglutarate-dependent dioxygenases, such as DNA demethylases and histone, which could result in significant epigenetic alterations.[47]

Recently, vitamin D has attracted a lot of attention as a potential cancer preventative, notably regarding breast, colorectal, and prostate cancers. Breast cancer patients often have vitamin D deficiency, and some data indicates that this condition may increase the risk of cancer progression.[48] Numerous findings have come from observational studies on calcium and cancer prevention. A relationship between increased calcium consumption and a lower risk

Table 1. Few polyphenols, plant sources, and their chemical formula

Polyphenols	Vegetal sources
Resveratrol	Red grapes, blueberries, berries wine, peanuts, soy, etc.
Apigenin	Parsley, chamomile, celery, vine spinach, artichokes, oregano, etc.
Genistein	Soy-based foods
Lycopene	Tomatoes, strawberries, cherries, pomegranate, watermelon, papaya pink grapefruit, apricots, red oranges, etc.
Curcumin	Turmeric
Epigallocatenin gallate	White, green, and black tea, apples, blackberries, raspberries, pecans, hazelnuts, peaches, avocados, pistachios, onions, etc.
Oleuropein	Olive, olive oil

of breast cancer was supported by a meta-analysis of observational data. Results for prostate cancer, however, have been contradictory, with numerous observational studies indicating an elevated risk for prostate cancer with larger calcium intakes.[49] Song and Garrett[50] observed that predominant data points to a higher risk of colorectal cancer in people who consume less calcium than 700–1,000 mg per day. Retinoids may have an impact on cancer because they directly affect cancer cells, inhibiting cell growth and causing differentiation and apoptosis. DNA mutations are induced by reactive oxygen species, which cause abnormal cell proliferation that induces tumor growth. Vitamin A (retinoids and carotenoids) has the ability to keep the cellular equilibrium between antioxidant and pro-oxidant molecules in cells, neutralizing nitrogen and oxygen free radicals (de Carvalho et al., 2019). It was stated that breast cancer in humans and animal models could both be inhibited by retinoids.[51] The dose/concentration employed, the selected target tissue, the experimental models, as well as medicational interactions that may have positive or negative effects on the body's redox state all influence the promotion of antioxidant effects by retinoid compounds in cell lines or living organisms.[52] A study found that β-carotene from food and supplements had diverse impacts on the likelihood of developing lung cancer, with food reducing risk and supplements raising it. Also, β-carotene supplementation was found to increase the risk of lung cancer in smokers regardless of the nicotine and tar content of cigarettes, indicating that smokers should refrain from taking this vitamin as a supplement unless they have vitamin A deficiency.[53]

Meng, Sun[54] reported that high dietary intakes of calcium and magnesium were linked to a lower risk of colorectal cancer, according to a meta-analysis of cohort studies. However, high dietary consumption of iron was positively connected with an increased risk of colorectal cancer. Magnesium and calcium, which are both members of the same family in the periodic table, share a homeostatic regulatory system and have the ability to physiologically conflict with one another. High calcium consumption decreases both magnesium and calcium absorption, whereas mild magnesium deprivation causes a negative magnesium balance but increases calcium retention.[55] It is anticipated that the dietary calcium to magnesium ratio may alter the effects of calcium supplementation on colorectal carcinogenesis owing to the potential for antagonism between magnesium and calcium.[54]

Plant Polyphenols

Various polyphenol varieties are known to exist thus adding complexity to a thorough description of any single plant, and making polyphenols one of the broadest categories of plant constituents. Moreover, its applications in cancer therapy have been previously discussed by various researchers. A basis for further research and the formulation of new polyphenol-based health nutrition products has been laid by the introduction of some commercialized functionalized polyphenol products to the market. Plant metabolism produces polyphenols, which are abundant in foods like fruits, vegetables, spices, soy, nuts, and beverages with plant origins. Based on their structural characteristics, they can be categorized into five classes: flavonoids, phenolic acids, lignans, stilbenes, and other polyphenols (Table 1). The main polyphenols found in plants are flavonoids and phenolic acids, which make up about 30% and 60% of all naturally occurring polyphenols, respectively. Some forms of cancer are well-protected against polyphenols: They have toxic effects on cells that can limit the growth of tumors and that cause apoptosis. An effective strategy for cancer prevention is a multifaceted approach that targets different pathways involved in cancer initiation and progression. The scientific community faces challenges in developing strategies and medications for cancer, due to hurdles including drug resistance and the side effects of chemotherapy. Polyphenols appear to be effective chemopreventive drugs due to a number of protective actions they exhibit, including cell cycle signaling modification, activation of antioxidant enzymes, apoptosis, and cell cycle arrest.[56] The studies that originally proposed polyphenols' anti-cancer properties were epidemiological. According to a study done on males in 59 different nations, eating soy products like tofu significantly decreased the incidence of prostate cancer.[57] Additionally, a study suggests that drinking tea considerably lowers the incidence of breast cancer.[58] Food polyphenols can also induce apoptosis in cancer cells such as breast carcinoma cell line (MCF-7), human laryngeal epithelioma cell line (HEp2), human cervical cancer cell line (HeLa), human hepatoma cell line (HepG2), human hepato-cellular liver carcinoma cell line (HepG2), acute myeloid leukemia cell line (AML).[59] Some of the phytochemicals, such as piperine, curcumin, indole-3-carbinol, quercetin, sulforaphane, and epigallocatechin gallate have been reported to have antitumoral effects against breast cancer and breast cancer recurrence by preventing its growth, invasion, metagenesis, and angiogenesis.[41]

Lee and Lee[60] conducted an *in vitro* study using prostate carcinoma LNCaP cells and reported that resveratrol possesses strong antioxidant qualities and has the ability to decrease cell growth and induce apoptosis, which can all have an impact on how cancer and other related disorders progress. *In vitro* studies on pancreatic cancer cell lines such as PANC-1, BxPC-3, and MiaPaCa-2 show that quercetin administration reduces the viability or proliferation of these cells in a dose- and/or time-dependent manner providing evidence for its chemopreventive characteristics.[61,62] Numerous more research programs have also supported polyphenols' anticancer

potential. Known for its potential antioxidant and hepatoprotective properties, silymarin is a complex extract that is extracted from the plant *Silybum marianum*. However, growing data also points to its exceptional antiproliferative and apoptotic properties.[63] Silymarin has had strong preventive and therapeutic actions against liver disorders and has been proven to cause apoptosis in liver cancer cells. Due to liver toxicity, chemotherapy is frequently discontinued during administration, especially during the maintenance phase of treatment. Milk thistle extract (80–240 mg/day) was given orally to the treatment group during a 56-day double-blind research in children with acute lymphoblastic leukemia (ALL) and liver toxicity, and silymarin was found to reduce the frequency of hepatic toxicity in ALL chemotherapy regimens.[64] In a randomized, double-blind pilot study that assessed the impact of adding silymarin (420 mg/day) to standard chemotherapy on the clinical response of advanced malignancies following three cycles of cisplatin-based chemotherapy, a tendency of decreased metastasis rate in the chemotherapy plus silymarin group was reported though there was no significant variance in tumor size.[65] Epigallocatechin gallate has also demonstrated favorable anticancer effects on breast cancer and numerous studies have demonstrated that curcumin inhibits the growth and spread of cancer cells while also causing cell cycle arrest and apoptosis.[66,67] In a study by Braicu and Gherman,[68] the researchers showed that EGCG (20 μM) prevented breast cancer cells (Hs578T) from proliferating after 48 and 72 hours of treatment, primarily through inducing apoptosis. Various polyphenols and their mechanisms for cancer inhibition are discussed below.

Numerous researches conducted over the past few years have shown that curcumin inhibits cell growth, metastasis, and proliferation while causing cell death in a variety of malignancies. Additionally, curcumin displays anti-cancer properties.[69,70] Patients in a phase 2 clinical trial employing curcumin in 21 patients with advanced pancreatic cancer demonstrated clinical indications of tumor regression after receiving 8 g/day of curcumin orally for 8 weeks.[71] Natural killer cell activity in rats was unaffected by curcumin supplementation in some early trials when given at levels up to 40 mg/kg for up to five weeks. However, Yadav and Mishra[72] investigated the immunomodulatory properties of curcumin in a different study and demonstrated that this substance can boost natural killer cell cytotoxicity in vitro. A critical area for research is the extent of the anticancer effects and apoptosis induction by curcumin. Through intrinsic or mitochondrial mechanisms, apoptosis takes place. Regardless of the route, changes in membrane potential and protein release are significant apoptotic events. By interacting with reactive oxygen species, curcumin may activate apoptotic pathways. For instance, human lung adenocarcinoma epithelial cells exposed to curcumin had higher quantities of reactive oxygen species and superoxide radicals. Moreover, reactive oxygen species, which activate apoptotic pathways in cancer cells, may be generated by curcumin and it may also raise intracellular calcium levels, which help trigger apoptosis by altering the poetics of cell membranes. In the human lung cancer cell line A54, curcumin acts on the Wnt/β-catenin-dependent pathway to demonstrate its therapeutic potential in the treatment of lung cancer.[73] With regard to combating the widespread medication resistance that is present in many cancer types, including breast cancer, curcumin has demonstrated encouraging effects. For instance, cisplatin resistance is promoted by the overexpression of Flap endonuclease 1in breast cancer cell lines. By inhibiting Flap endonuclease 1 expression in vitro, curcumin was reported to increase the sensitivity of breast cancer cells to cisplatin.[74] In a phase 1/2 trial, 29 patients with multiple myeloma (MM) were given oral dosages of curcumin alone (2, 4, 6, 8, or 12 g/day in two divided doses) or together with Bio-Perine (10 mg/day) for a period of 12 weeks. The study found that the combined treatment was more efficient than bioperine alone and that curcumin was not linked to any adverse effects.[75] The poor water solubility and poor absorption of curcumin, however, prevent its widespread use as an anticancer treatment and the bioavailability of curcumin remains incredibly low. Additionally, it is subject to limited absorption by the small intestine and fast elimination by the gallbladder and its oral bioavailability is minimal. However, as an individual treatment and in combination with other antineoplastic medicines, curcumin has demonstrated promising effects in the treatment of several cancers: It has an impact on several signaling pathways and can therefore successfully alter both the initiation and progression of certain cancers (Zoi et al., 2021).

Due to its low intrinsic toxicity and unique effects on cancer cells when compared to other structurally comparable flavonoids, apigenin, a consumable flavonoid, has gained popularity as a health-promoting medication in recent years.[76] It can be found in a variety of fruits and vegetables as well as drinks including tea and wine as well as in parsley, celery, chamomile, and oranges.[77] Apigenin's potent antioxidant and anti-inflammatory properties are a significant factor in its potential cancer-preventive actions. More significantly, apigenin induces apoptosis in a variety of cell lines and animal models, contributing considerably to the prevention of cancer.[78,79] In one in-vitro investigation, apigenin demonstrated a strong growth-inhibitory effect in breast cancer cells and caused apoptosis in neu/HER2 overexpressing breast cancer cells.[80] According to dose and time, apigenin inhibited cancer cell proliferation and encouraged cell death. Apoptosis and autophagy are both induced by apigenin through the suppression of the PI3K/Akt/mTOR pathway.[81] In numerous cancer models, including pancreatic cancer, the flavonoid quercetin has also been thoroughly investigated for its anti-cancer properties. According to several pieces of research, quercetin has a systemic anti-tumor action and increases chemotherapy effectiveness through its easily digestible and accessible qualities.[82] However, to find out whether quercetin can also speed up the digestion and absorption of chemotherapeutic drugs, more research is necessary. Similar to quercetin, resveratrol, another polyphenol, is found in a wide variety of fruits. It has been studied for its potent antioxidant properties in a variety of disease models, including cancers.[83] The most bioactive catechin that is primarily found in tea is epigallocatechin gallate (EGCG). The usage of this catechin in preclinical models has been associated with a wide range of biomolecular pathways that have been shown to be active. Apoptosis induction, cell cycle changes, antioxidant activity, modification of enzymes involved in drug metabolism, etc. are a few examples of these, although it is not restricted to them. Depending on the kind of cancer cell, EGCG has a variety of pharmacological effects that reflect various protein expressions and epigenetic pathways. Every cell model can express and modify its genetic background as needed, which is the basis for the various biomolecular targets that EGCG activates. Notably, EGCG has been studied in various tumor cell lines and less frequently in animal models. Isothiocyanates (ITCs) are bioactive substances found in cruciferous vegetables such as broccoli, cauliflower, watercress, and mustard. Consumption of cruciferous vegetables was found to reduce the incidence of colorectal cancer in a case-control study of Shanghai women (322 cases and 1,251 controls).[84] In this case-control study, which included 694 newly diagnosed patients and 708 controls, it was discovered that cruciferous vegetable consumption was associated with a 29% lower chance of developing bladder cancer. In addition, people who consumed three or more servings of cruciferous vegetables per week had a 32% lower risk of lung cancer than people who consumed one-half serving or

less.[85,86]

Besides micronutrients and phytochemicals, probiotics are another group of functional food that provides potential cancer prevention. Several studies have demonstrated the potential of probiotics in cancer prevention through various mechanisms including modification of microbiota, neutralization of carcinogens, vitamin and short-chain fatty acids synthesis, improved gut barrier function, inhibition of cell proliferation, cell apoptosis, and anti-inflammatory and anti-pathogenic activity with effects on lowering tumor growth and metastasis.[87] In a study by Shang and Jiang,[88] the authors reported that a probiotic mixture had the potential to inhibit colorectal cancer through the significantly repressed invasion, proliferation, and migration ability of CT26 cells when compared to control cells. Isazadeh and Hajazimian[89] revealed that *L. acidophilus* supernatant and extract could increase the survival rate of colon cancer patients by reducing the viability and proliferation of the Caco-2 colorectal cancer cell line. Similarly, probiotics have been demonstrated to have pro-apoptotic and anti-proliferative activities against gastrointestinal cancer with colonic cancer cells and gastric cancer cells being the most frequently researched.[90] Moreover, postbiotics are a broad category of complex macromolecules that include inactivated microbial cells, cellular fractions, and metabolites. They have the ability to modulate the immune system and possess anticancer properties by inducing apoptosis, inhibiting proliferation, and reducing inflammation.[91]

Conclusion

People are more susceptible to diet-related illnesses and cancers as a result of changes in lifestyle and eating habits. Additionally, it is well-established that dietary changes greatly lower the risk of illnesses. Cancer risk can be lowered by following a healthy and balanced diet. It is well known that a diet high in fruits and vegetables protects against the emergence and progress of cancer and the positive effects are usually thought to be caused, at least in part, by polyphenols and other dietary supplements. However, excluding particular foods will not lower the risk of developing cancer, and the same applies to any diet or food group. But, consuming a diet rich in nutrients including fruits, whole grains, legumes, and vegetables can help to lower the risk of developing cancer and other chronic diseases. The antioxidants (present in fruits, vegetables, and nuts) help to repair cells, have anti-inflammatory properties, and reduce excessive free radical formation in the body, which is the main mechanism of action of cancer cells. The data from epidemiological, preclinical, and clinical research have made a significant contribution to the knowledge connecting diet and cancer prevention. However, there is only a limited understanding of the fundamental relationship between diet and cancer prevention. Also, dietary supplements should not be administered indiscriminately as they may have positive or negative effects and the literature also shows inconsistencies. Cancer research is challenging, and it is never easy to determine the true impact of just one of these factors because several lifestyle factors also have an impact on the risk of cancer. This is an important point regarding the efficacy of diet and supplements in the prevention of cancer. There is currently no conclusive evidence in favor of any one dietary regimen for lowering the risk of cancer. Although not conclusive, the results of various studies indicate that general dietary modification has a positive impact on the prevention of cancer. However, caution must be exercised to prevent excessive dietary supplement usage as it could be harmful. Diet and dietary supplements enable cancer patients to actively participate in their care; however, it is important to make sure that the patient is aware of both the risks associated with forgoing proven conventional treatments as well as the minimal impact that diet and supplements will have on cancer control.

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Conflict of interest

KS is an employee of Sargento Foods. The authors have no other conflict of interests related to this publication.

Author contributions

ACK, PT, KSB, and KS searched and collected literature, compiled data, and drafted the manuscript. MSR and SN revised and edited the manuscript. NPN conceive the work, revised and edited the manuscript, supervised, and project administration. All authors are agreed in their accountable contributions and approval of the manuscript.

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